Current Therapeutic Research

Volume 69, Number 5, October 2008

Kanglaite Injection Plus Chemotherapy Versus Chemotherapy Alone for Non–Small Cell Lung Cancer Patients: A Systematic Review and Meta-Analysis

Xuemei Liu, PhD[1]; Feng Xu, MD[2]; Gang Wang, PhD[3]; Xiang Diao, MD[4]; and Youping Li, MD[1]

[1]Chinese Cochrane/Evidence-Based Medicine Center, Chinese Journal of Evidence-Based Medicine, Periodical Press of West China Hospital of Sichuan University, Chengdu, China; [2]Department of Oncology, Periodical Press of West China Hospital of Sichuan University, Chengdu, China; [3]Department of Integrated Chinese and Western Medicine, West China Hospital of Sichuan University, Chengdu, China; and [4]Chinese Journal of Evidence-Based Medicine, West China Hospital of Sichuan University, Chengdu, China

ABSTRACT

Background: Kanglaite (KLT) is a botanically sourced, molecularly targeted agent that is prepared as a microemulsion for IV use. The active substance is extracted from the herb *Semen coicis*.

Objective: The aim of this study was to evaluate the effectiveness and tolerability of KLT injection in patients with primary non–small cell lung cancer (NSCLC).

Methods: We electronically searched the literature of the China National Knowledge Infrastructure (Chinese language, 1979–March 2008), CBMdisc (Chinese, 1978–March 2008), The Cochrane Library (English, Issue 4, 2007), MEDLINE (English, 1966–March 2008), and EMBASE (English, 1984–March 2008), and manually searched 20 Chinese-language oncology journals to identify randomized controlled trials (RCTs) of KLT injection plus chemotherapy versus chemotherapy alone, regardless of their having been published or not, blinding, duration of treatment, or duration of follow-up. The quality of the included trials was assessed using the method recommended by The Cochrane Collaboration. The studies were assigned to 1 of the following 3 categories: A = all quality criteria met, low risk of bias; B = ≥1 of the quality criteria only partially met, moderate risk of bias; or C = ≥1 of the quality criteria not met, high risk of bias. If heterogeneity existed among subgroups, then overall results were calculated based on a random-effects model; otherwise, a fixed-effects model was used.

Results: Electronic database searches yielded 596 citations. A title review eliminated 377 manuscripts; 219 citations were marked for further evaluation. Finally, we identified 26 trials that met the inclusion and exclusion criteria. The 26 RCTs included in this meta-analysis included 2209 patients with NSCLC; no study was graded A, 9 were graded B, and 17 were graded C. The sample size of each trial varied from 40 to 305 patients; none of the trials had precalculated sample sizes. Pooled

Accepted for publication June 23, 2008.

doi:10.1016/j.curtheres.2008.10.004

0011-393X/$32.00

analyses performed using both fixed- and random-effects models revealed that compared with chemotherapy alone, KLT injection plus chemotherapy improved the response rate (relative risk [RR], 1.34; 95% CI, 1.19–1.51 and RR, 1.35; 95% CI, 1.20–1.51, respectively) and quality of life as measured by an increase ≥10 points in the Karnofsky Performance Status score (RR, 2.05; 95% CI, 1.60–2.64). KLT injection plus chemotherapy was associated with improvement in the symptoms of cough, dyspnea, chest pain, fatigue, and anorexia. KLT injection plus chemotherapy was also associated with significant reduction in the incidence of the following adverse events (AEs) based on the fixed and random effects models, respectively: grade II to IV leukopenia (RR, 0.29; 95% CI, 0.22–0.39 and RR, 0.33; 95% CI, 0.22–0.48), anemia (RR, 0.54; 95% CI, 0.42–0.70 and RR, 0.55; 95% CI, 0.40–0.76), thrombocytopenia (RR, 0.39; 95% CI, 0.21–0.71 and RR, 0.40; 95% CI, 0.21–0.78), nausea and vomiting (RR, 0.44; 95% CI, 0.34–0.57 and RR, 0.44; 95% CI, 0.35–0.57), phlebitis (RR, 3.44; 95% CI, 1.30–9.15 and RR, 3.38; 95% CI, 1.28–8.89), and hepatic dysfunction (RR, 0.44; 95% CI, 0.15–1.35 and RR, 0.44; 95% CI, 0.24–0.81).

CONCLUSION: This meta-analysis found that KLT injection in combination with chemotherapy was associated with improved response rate, quality of life, and symptoms, and a reduced incidence of AEs compared with chemotherapy alone in patients with NSCLC. These findings should be viewed with caution because of the low quality of the included trials. (*Curr Ther Res Clin Exp.* 2008;69:381–411) © 2008 Excerpta Medica Inc.

KEY WORDS: kanglaite injection, non–small cell lung cancer, systematic review.

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the United States.[1] In 2005, 172,570 new cases of lung cancer were diagnosed and 163,510 resulted in death. When lung cancer patients are found unsuitable for surgery at diagnosis, chemotherapy remains a treatment option. Histologically, ~80% of these tumors are of the non–small cell type, including adenocarcinomas and squamous cell and large cell carcinomas. Non–small cell lung cancer (NSCLC) is the main cause of cancer-related deaths.[1] In advanced-stage NSCLC, chemotherapy prolongs survival and improves patient quality of life, but its effectiveness is not completely satisfactory.

Kanglaite (KLT) (Zhejiang Kanglaite Group Co. Ltd., Hangzhou, China) is a botanically sourced, molecularly targeted agent that is prepared as a microemulsion for IV use. The active substance is extracted from the herb *Semen coicis*. It is used in combination with chemotherapy to minimize toxic reactions and enhance the effect of chemotherapy. In 1995, KLT patent certificates were granted in China. In August 1997, Phase III clinical trials were completed and KLT was officially launched in China after final approval from the Ministry of Public Health.[2] Since 1997, >500,000 cancer patients in >2000 large- and medium-sized hospitals in China have been treated with KLT.

A *Semen coicis* extract was found to suppress the growth of squamous lung cancer cells.[3] KLT decreased the number of G2/M phase cells, suppressed the proliferation of cancer cells, and induced apoptosis of cancer cells, actions that constitute an important mechanism of the antitumor action of KLT.[4] KLT was found to be effective in reversing multiple-drug resistance of cells and increasing the sensitivity of mouse cancer cells to chemotherapeutic agents.[5] KLT injection might have a direct effect on cancer cell death and improvement of patients' immune function, symptoms, and quality of life.[6]

A Cochrane protocol focused on symptom palliation of patients with lung cancer rather than effectiveness.[7] To date, no systematic review or meta-analysis of the effectiveness of KLT injection in patients with primary NSCLC has been done.

The aim of this meta-analysis was to evaluate the effectiveness and tolerability of KLT injection plus chemotherapy versus chemotherapy alone for patients with NSCLC.

MATERIALS AND METHODS

STUDY DESIGN

Only randomized controlled trials (RCTs) were eligible for this review; blinding, language, published or not, duration of treatment, and the duration of follow-up were not considered. Uncontrolled and observational studies were excluded.

PATIENTS

Patients were eligible for the study if they had primary NSCLC that was confirmed cytologically, pathologically, or by computed tomography or if they had inoperable stage II to IV cancer or stage II cancer and had refused surgery. Patients with a Karnofsky Performance Status (KPS) score[8] ≥50 and an expected survival time of ≥3 months who were aged ≥18 years were also eligible. Finally, patients not treated with chemotherapy or radiotherapy who had not participated in a trial for ≥2 months were also eligible.

Patients were excluded from the study if they had liver, brain, or bone metastasis (although asymptomatic patients were eligible); severe heart, hepatic, or renal disease; markedly abnormal blood biochemistry findings; or hepatic or renal dysfunction. Patients who had just undergone surgery or radiotherapy treatment were also excluded.

INTERVENTIONS

The trial groups received KLT injection plus chemotherapy and the control groups received chemotherapy alone, regardless of the duration of treatment or follow-up. The basic treatment in both trial and control groups was identical except for KLT injection.

OUTCOME MEASURES

Mortality Rate

Mortality rate at the end of treatment or follow-up was calculated.

Response Rate

Response Evaluation Criteria in Solid Tumors, formulated by the World Health Organization (WHO), was used to evaluate the response rate.[9] Based on the degree of tumor absorption, *response* was classified as follows: (1) *complete response* (CR) = chest radiograph or computed tomography and/or fiber bronchoscopy revealed complete absorption of the lesion; (2) *partial response* (PR) = lesion decreased by ≥50% but ≤99%; (3) *no change* = lesion decreased by <50% or increased by <25%; and (4) *progressive disease* = lesion increased by >25% after treatment. Based on the comparison of chest radiograph or computed tomography before and after treatment, the *response rate* was defined as CR + PR.[8]

Quality-of-Life Improvement

Quality of life before and after treatment was assessed using the KPS. Only data for patients whose KPS scores improved by ≥10 points (the minimal clinically significant difference) after treatment were extracted.

Symptom Improvement

The percentage of patients exhibiting improvement in the symptoms of cough, hemoptysis, chest pain, fever, fatigue, and anorexia was assessed. We also calculated the percentage of patients whose symptoms resolved completely. Improvement in symptoms was assessed according to the information provided in each included study.

Specifically, for the pooled analysis of the trials in which symptom improvement was reported, symptoms were scored according to their degree of severity (ie, grades I–III). For the symptoms of cough, chest pain, and dyspnea, grade I was assigned when the symptoms did not influence daily life, and grade III was assigned when the symptoms were severe, with a marked influence on daily life; symptoms between grade I and III were assigned grade II. For hemoptysis, sputum with blood was assigned grade I, sputum with blood clots or sputum with ≤10 mL/d of blood was assigned grade II, and extremely bloody sputum or sputum with >10 mL/d of blood was assigned grade III. A reduction of more than two thirds in the total score of clinical symptoms was considered improvement, a reduction of no more than two thirds but greater than one third was considered partial improvement, and an unchanged total score or a reduction of no more than one third was considered stable disease.

ADVERSE EVENTS

Adverse events (AEs) were evaluated at the completion of treatment and included bone marrow suppression (leukopenia, anemia, and thrombocytopenia), nausea and vomiting, phlebitis, hepatic dysfunction, and renal dysfunction. According to the WHO grading criteria for acute and subacute toxicity of anticancer drugs,[10] we only calculated AEs of grades II to IV. If patients withdrew from the study due to an AE, we also included these AEs.

LITERATURE COLLECTION

We electronically searched literature of the China National Knowledge Infrastructure (Chinese language, 1979–March 2008), CBMdisc (Chinese, 1978–March 2008), The Cochrane Library (English, Issue 4, 2007), MEDLINE (English, 1966–March 2008), and EMBASE (English, 1984–March 2008). The reference lists of relevant trials were obtained. We also collected data from ongoing trials documented in Current Controlled Trials (www.controlled-trials.com) and Clinical Trials (www.clinicaltrials.gov). In addition, we manually searched the following 20 Chinese oncology journals up to March 2008: *Chinese Journal of Lung Cancer* (1998–March 2008), *Chinese-German Journal of Clinical Oncology* (1984–March 2008), *Chinese Journal of Cancer Research* (1989–March 2008), *Journal of Practical Oncology* (1987–March 2008), *Journal of Modern Oncology* (1993–March 2008), *Tumor* (1981–March 2008), *Journal of Oncology* (1995–March 2008), *Chinese Journal of Cancer* (1987–March 2008), *Chinese Clinical Oncology* (1985–March 2008), *Journal of Practical Oncology* (1986–March 2008), *Bulletin of Chinese Cancer* (1992–March 2008), *Chinese Journal of Clinical Oncology and Rehabilitation* (1994–March 2008), *Chinese Journal of Cancer Prevention and Treatment* (1994–March 2008), *Cancer Research on Prevention and Treatment* (1973–March 2008), *Oncology Progress* (2003–March 2008), *Journal of International Oncology* (1974–March 2008), *Practical Journal of Cancer* (1985–March 2008), *Sichuan Journal of Cancer Control* (1973–March 2008), *Chinese Journal of Oncology* (1979–March 2008), and *Chinese Journal of Integrated Traditional and Western Medicine* (1981–March 2008).

QUALITY ASSESSMENT AND DATA EXTRACTION

Trial Selection

To select eligible studies, one author (X.L.) independently reviewed the title, abstract, and key words of every retrieved record, and another author (G.W.) checked the results. Full-text articles were retrieved for further assessment if the information available suggested that the study: (1) included patients with NSCLC; (2) compared KLT injection plus chemotherapy with chemotherapy alone; (3) randomly assigned patients to the comparison groups; and (4) included the outcome measures listed previously. Differences were resolved by discussion.

Quality Assessment

The quality of the trials was assessed according to the Cochrane Collaboration's criteria[11]: (1) minimization of selection bias (ie, were the randomization procedure and the allocation concealment adequate); (2) minimization of performance bias (ie, were the patients who received treatment and people who administered the treatment blinded to the interventions); (3) minimization of attrition bias (ie, were withdrawals and dropouts completely described and was the analysis based on intent to treat [ITT]); and (4) minimization of detection bias (ie, were outcome assessors blinded to the interventions). Based on these criteria, the studies were broadly subdivided into the following 3 categories: A = all quality criteria met, low risk of bias; B = ≥1 of the quality criteria only partially met, moderate risk of bias; and C = ≥1 criteria not met, high risk of bias.

Each trial was assessed independently by one author (X.L.) and was checked by another author (G.W.). Differences were resolved by discussion.

Data Extraction

Data from each included trial were extracted independently by one author (X.L.) and checked by another author (G.W.) using a standard extraction form. The form included the following items:

- General information: published/unpublished; language; authors; article title; journal title, year, volume, issue, and page numbers; and funding source;
- Trial design: predetermined sample size, generation of randomization sequence, allocation concealment method, blinding of information, statistical methods, and attrition;
- Participants: diagnostic criteria, total number of patients and number of patients in the comparison groups, baseline characteristics (eg, age, gender), inclusion criteria, exclusion criteria, and study settings;
- Intervention: type of chemotherapy regimen, duration, time, and dose; co-intervention; control; withdrawals, dropouts, and lost to follow-up; and
- Outcome: outcomes at the end of treatment.

The number and type of AEs were also extracted. If the aforementioned data were not available in the trial report, further information was sought by corresponding with the original principal investigator.

Data Analysis

Data were analyzed using MetaView 4.2.8 in Review Manager 4.2 (Cochrane collaboration, Oxford, United Kingdom). Meta-analysis was conducted by pooling the different chemotherapy regimens combined with KLT injection and comparing these with chemotherapy regimens alone for an overall analysis; however, the analysis was divided according to subgroups that were formed based on chemotherapy regimens. Sensitivity analyses were conducted by excluding low-quality trials. Analyses were conducted using the ITT principle when possible. Relative risk (RR) was used to analyze dichotomous data. If heterogeneity existed among subgroups, then overall results were calculated based on the random effect model; otherwise, the fixed effect model was used. The random effect model was also used to check whether its use might change the direction of the results in cases where heterogeneity was not tested. Heterogeneity was tested using the z score and χ^2, and $P < 0.1$ was considered statistically significant.

RESULTS

Electronic database searches yielded 596 citations. A title review eliminated 377 manuscripts; 219 citations were marked for further evaluation. Finally, we identified 26 trials[12–37] that met the inclusion and exclusion criteria. All of the included studies were published in China. A diagram of the meta-analysis is shown in **Figure 1**.

CHARACTERISTICS OF THE INCLUDED TRIALS

All of the included trials met the inclusion criteria. The baseline characteristics of the trial and control groups in the included trials were comparable. All the patients in the included trials had NSCLC that was confirmed cytologically or pathologically.

Interventions and outcome measures used in the included trials are listed in **Table I**.[12–37] No trial reported the outcome measure of mortality.

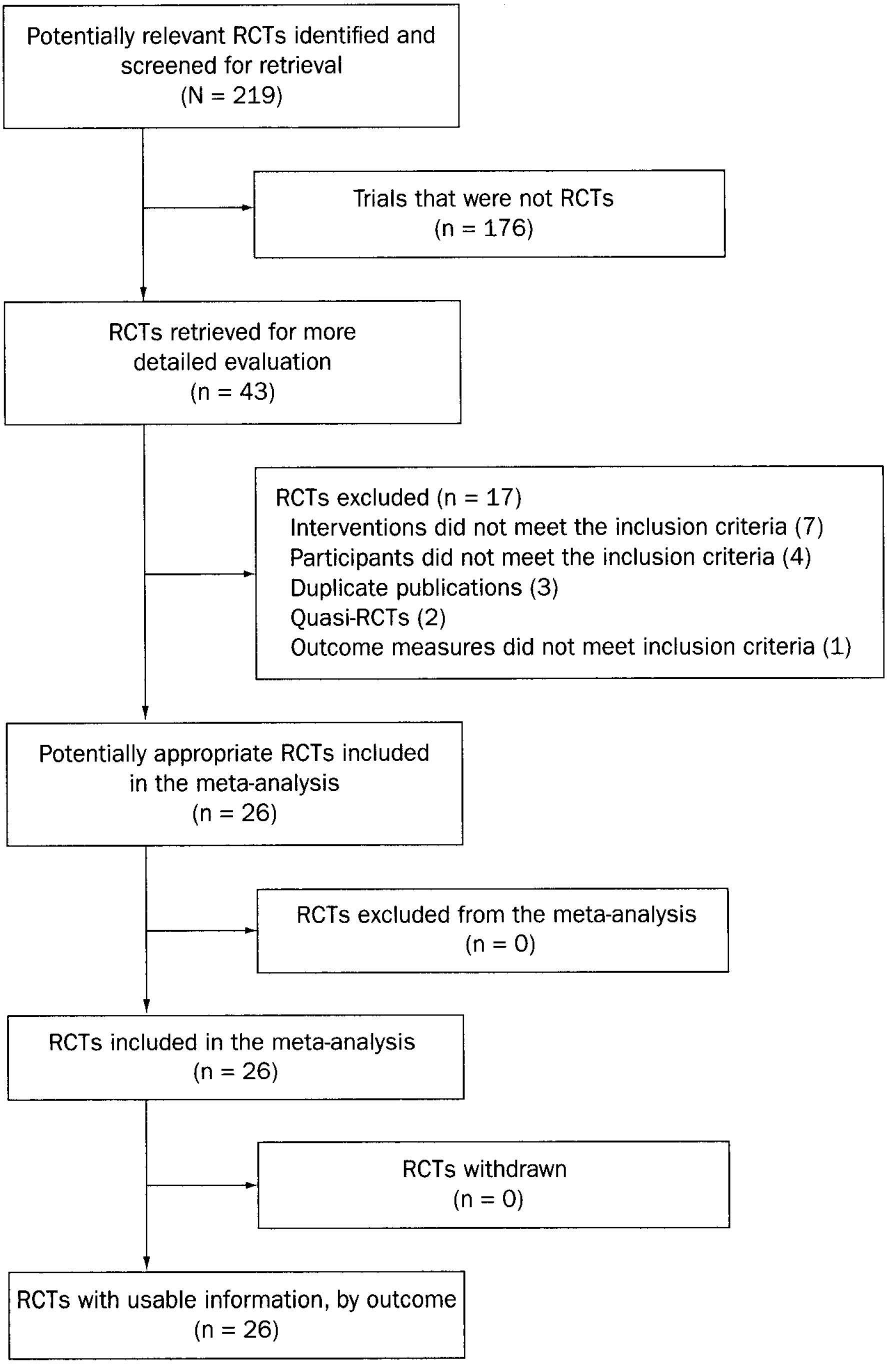

Figure 1. Flow diagram of the meta-analysis. RCTs = randomized controlled trials.

Table I. Characteristics of the included trials (N = 26).

Reference	No. of Cases, Trial/Control	Interventions		Outcome Measures	Duration, d
		Trial Group	Control Group		
Piao et al[12]	214/91	KLT + MVP or EP	MVP or EP	Response rate, KPS score improved ≥10 points, symptom improvement	42
Chu et al[13]	40/32	KLT + MVP	MVP	Response rate, anemia	28
Li and Wang[14]	34/30	KLT + MVP	MVP	Response rate, KPS score improved ≥10 points, gastrointestinal reaction, hepatic and renal dysfunction	14
Yang et al[15]	28/29	KLT + NP	NP	Response rate, KPS score improved ≥10 points	14
Chen et al[16]	28/27	KLT + NP	NP	Response rate, KPS score improved ≥10 points, leukopenia	14
Tang[17]	20/22	KLT + HEP	HEP	Response rate, KPS score improved ≥10 points, bone marrow suppression, gastrointestinal tract reaction, phlebitis	14
Xie et al[18]	43/44	KLT + NP	NP	KPS score improved ≥10 points	60
Liu et al[19]	131/111	KLT + MAP or MVP	MAP or MVP	Response rate, KPS score improved ≥10 points, symptom improvement	42
Lin et al[20]	39/41	KLT + CAP	CAP	Response rate, KPS score improved ≥10 points, bone marrow suppression, gastrointestinal reaction, phlebitis, hepatic and renal dysfunction	42
Lian et al[21]	50/50	KLT + GP	GP	Response rate, gastrointestinal tract reaction, hepatic and renal dysfunction	10
Deng et al[22]	21/22	KLT + GP	GP	Response rate, KPS score improved ≥10 points, bone marrow suppression, gastrointestinal reaction, phlebitis, hepatic and renal dysfunction	21

(continued)

Table I (continued).

Reference	No. of Cases, Trial/Control	Interventions		Outcome Measures	Duration, d
		Trial Group	Control Group		
Lu[23]	62/51	KLT + NP or GP	NP or GP	Response rate, KPS score improved ≥10 points, bone marrow suppression, gastrointestinal reaction	20–45
Lv et al[24]	30/30	KLT + NP	NP	Response rate, KPS score improved ≥10 points	21
Wu et al[25]	39/44	KLT + NP	NP	Response rate	42
Wu et al[26]	21/19	KLT + EP	EP	Response rate, KPS score improved ≥10 points, bone marrow suppression	10
Huang et al[27]	53/33	KLT + EP	EP	Response rate, KPS score improved ≥10 points, bone marrow suppression, gastrointestinal reaction, symptom improvement	42–63
Li et al[28]	36/36	KLT + NP	NP	Response rate, KPS score improved ≥10 points, bone marrow suppression, gastrointestinal reaction	21
Li et al[29]	20/20	KLT + NP	NP	Response rate, bone marrow suppression, phlebitis	42
Liu et al[30]	32/32	KLT + CEP	CEP	Bone marrow suppression, gastrointestinal reaction	56
Chen[31]	30/34	KLT + MVP	MVP	Response rate, KPS score improved ≥10 points	20
Song et al[32]	26/21	KLT + CAP	CAP	KPS score improved ≥10 points	42
Wang and Zhang[33]	39/41	KLT + NP	NP	Response rate, bone marrow suppression, gastrointestinal reaction, phlebitis, renal dysfunction	42
An and Yuan[34]	48/48	KLT + NP	NP	Response rate, symptom improvement	10

(continued)

Table I (continued).

Reference	No. of Cases, Trial/Control	Interventions		Outcome Measures	Duration, d
		Trial Group	Control Group		
Ju et al[35]	48/48	KLT + MVP	MVP	Response rate	42
Zhong et al[36]	22/26	KLT + NIC	NIC	KPS score improved ≥10 points, symptom improvement	Unclear
Wang et al[37]	42/38	KLT + MVP/NP/TP	MVP/NP/TP	KPS score improved ≥10 points	10

KLT = kanglaite; MVP = mitomycin + vindesine + cisplatin; EP = cisplatin + etoposide (VP-16); KPS = Karnofsky Performance Status; NP = vinorelbine + cisplatin; HEP = hydroxycamptothecin + VP-16 + cisplatin; MAP = mitomycin + adriamycin + cisplatin; CAP = cyclophosphamide + adriamycin + cisplatin; GP = gemcitabine hydrochloride + cisplatin; CEP = cyclophosphamide + epirubicin + cisplatin; NIC = vinorelbine + ifosfamide + cisplatin; TP = thymidine phosphorylase.

Quality of the Included Trials

The quality of 17 trials was rated C, 9 trials[12,13,18–22,24,35] were rated B, and no trial was rated A. Randomization sequences were generated using a computer in 2 trials,[12,13] a random digital table in 4 trials,[18,20,22,35] and by drawing lots in 4 trials.[19,21,24,29] Four trials reported double blinding,[12,19,22,35] while 5 trials reported single blinding.[13,18,20,21,25] We obtained randomization details of the trials conducted by Piao et al[12] and Chu et al[13] from Zhejiang Kanglaite Group Co. Ltd. We requested additional information about randomization from the authors of all the included trials, and obtained randomization details from the authors of 5 trials.[20–22,24,29] The details are listed in **Table II**.[12–37]

Meta-Analysis Results

Response Rate

The details of the response rates are shown in **Figure 2**. Response rate was used as an outcome measure in 22 trials[12–17,19–31,33–35] (**Table I**). Heterogeneity was not detected among the subgroups ($P = 0.48$). Pooled analysis of 9 subgroups revealed that compared with chemotherapy alone, KLT injection plus chemotherapy improved the response rate using both fixed (RR, 1.34; 95% CI, 1.19–1.51) and random effect models (RR, 1.35; 95% CI, 1.20–1.51). Grade C trials were excluded from the sensitivity analysis. The results of the sensitivity analysis were consistent between the fixed (RR, 1.29; 95% CI, 1.07–1.55) and random effect models (RR, 1.33; 95% CI, 1.05–1.68).

A subgroup analysis of 5 trials[12,14,26,31,35] suggested that a regimen of KLT injection plus chemotherapy with a regimen of mitomycin with vindesine and cisplatin (MVP) was associated with greater improvement in the response rate (RR, 1.76; 95% CI, 1.34–2.31) than chemotherapy alone.

Another subgroup analysis of 2 trials[21,22] found that compared with chemotherapy alone, KLT injection plus chemotherapy with gemcitabine hydrochloride plus cisplatin (GP) was associated with greater improvement in the response rate (RR, 1.75; 95% CI, 1.16–2.64).

Subgroup analysis of 8 trials[15,16,24,25,28,29,33,34] found that compared with chemotherapy with vinorelbine plus cisplatin (NP), KLT injection plus NP was associated with greater improvement in the response rate (RR, 1.30; 95% CI, 1.07–1.59).

The improvement in the response rates (**Figure 2**) with KLT injection plus chemotherapy was not greater than that associated with chemotherapy alone in the following regimens: hydroxycamptothecin + etoposide (VP-16) + cisplatin (HEP); cyclophosphamide + adriamycin + cisplatin (CAP); GP/NP; MVP/cisplatin + VP-16 (EP); mitomycin + adriamycin + cisplatin (MAP)/MVP; cyclophosphamide + epirubicin + cisplatin (CEP); and EP.

Analyses of the MVP, GP, and NP chemotherapy regimen subgroups found a statistical difference between KLT injection plus chemotherapy and chemotherapy alone. Each subgroup included data from >2 trials, with a sample size ranging from 71 to 275. Meanwhile, the analyses of the other 7 subgroups did not show a statistical difference between the 2 groups with regard to the response rate. Each subgroup in-

Table II. Quality assessment of the included trials (N = 26).

Reference	Random Sequence Generation	Allocation Concealment	Blinding	Lost to Follow-Up/ Duration of Follow-Up	ITT	Study Quality[11]*
Piao et al[12]	Computer	Unclear	Double	Number lost to follow-up and reason for loss of follow-up were reported/19 months	Yes	B
Chu et al[13]	Computer	Unclear	Single	Number lost to follow-up was reported/19 months	Yes	B
Li and Wang[14]	Unclear	Unclear	Unclear	No loss of follow-up/35 months	Yes	C
Yang et al[15]	Unclear	Unclear	Unclear	Number lost to follow-up was reported/36 months	No	C
Chen et al[16]	Unclear	Unclear	Unclear	No loss of follow-up/60 months	Yes	C
Tang[17]	Unclear	Unclear	Unclear	No loss of follow-up/30 months	Yes	C
Xie et al[18]	Random digital table	Adequate	Single	6 Patients lost to follow-up/12 months	No	B
Liu et al[19]	Drawing lots	Envelope	Double	Number lost to follow-up and reason for loss of follow-up were reported/16 months	Yes	B
Lin et al[20]	Random digital table	Adequate	Single	No loss of follow-up/52 months	Yes	B
Lian et al[21]	Drawing lots	Envelope	Single	No loss of follow-up/17 months	Yes	B
Deng et al[22]	Random digital table	Adequate	Double	No loss of follow-up/36 months	Yes	B
Lu[23]	Unclear	Unclear	Unclear	No loss of follow-up/30 months	Yes	C
Lv et al[24]	Drawing lots	Adequate	Single	No loss of follow-up/34 months	Yes	B
Wu et al[25]	Unclear	Unclear	Unclear	No loss of follow-up/60 months	Yes	C
Wu et al[26]	Unclear	Unclear	Unclear	No loss of follow-up/24 months	Yes	C
Huang et al[27]	Unclear	Unclear	Unclear	No loss of follow-up/2.8 to 6.3 months	Yes	C
Li et al[28]	Unclear	Unclear	Unclear	No loss of follow-up/42 months	Yes	C
Li et al[29]	Drawing lots	Inadequate	No blinding	No loss of follow-up/24 months	Yes	C
Liu et al[30]	Unclear	Unclear	Unclear	No loss of follow-up/unclear	Yes	C
Chen[31]	Unclear	Unclear	Unclear	No loss of follow-up/32 months	Yes	C

(continued)

Table II (continued).

Reference	Random *Sequence* Generation	*Allocation* Concealment	Blinding	Lost to Follow-Up/ Duration of Follow-Up	ITT	Study Quality[11*]
Song et al[32]	Unclear	Unclear	Unclear	No loss of follow-up/117 months	Yes	C
Wang and Zhang[33]	Unclear	Unclear	Unclear	No loss of follow-up/53 months	Yes	C
An and Yuan[34]	Unclear	Unclear	Unclear	No loss of follow-up/24 months	Yes	C
Ju et al[35]	Random digital table	Adequate	Double	Number and reason for loss of follow-up were reported/18 months	No	B
Zhong et al[36]	Unclear	Unclear	Unclear	No loss of follow-up/unclear	Yes	C
Wang et al[37]	Unclear	Unclear	Unclear	No loss of follow-up/20 months	Yes	C

ITT = intention-to-treat.

*A = all quality criteria met, low risk of bias; B = ≥1 of the quality criteria only partially met, moderate risk of bias; C = ≥1 of the quality criteria not met, high risk of bias.

Study or Subcategory	KLT, n/N	Chemotherapy, n/N	RR (fixed), 95% CI	Weight, %	RR (fixed), 95% CI	Quality*
MVP + KLT vs MVP						
Ju et al[35]	16/48	12/48		4.08	1.33 (0.71–2.51)	B
Wu et al[26]	9/21	5/19		1.78	1.63 (0.66–4.01)	C
Chen[31]	24/30	16/34		5.10	1.70 (1.14–2.53)	C
Li and Wang[14]	19/34	9/30		3.25	1.86 (1.00–3.47)	C
Piao et al[12]	18/40	7/40		2.38	2.57 (1.21–5.47)	B
Subtotal (95% CI)	173	171		16.58	1.76 (1.34–2.31)	
Total events: 86 (KLT), 49 (Chemotherapy)						
Test for heterogeneity: $\chi^2 = 1.80$, $df = 4$ ($P = 0.77$), $I^2 = 0\%$						
Test for overall effect: $z = 4.06$ ($P < 0.001$)						
GP + KLT vs GP						
Lian et al[21]	26/50	16/50		5.44	1.63 (1.00–2.64)	B
Deng et al[22]	12/21	6/22		1.99	2.10 (0.96–4.55)	B
Subtotal (95% CI)	71	72		7.43	1.75 (1.16–2.64)	
Total events: 38 (KLT), 22 (Chemotherapy)						
Test for heterogeneity: $\chi^2 = 0.30$, $df = 1$ ($P = 0.59$), $I^2 = 0\%$						
Test for overall effect: $z = 2.68$ ($P = 0.007$)						
NP + KLT vs NP						
An and Yuan[34]	22/48	24/48		8.15	0.92 (0.60–1.39)	B
Yang et al[15]	9/28	10/29		3.34	0.93 (0.45–1.95)	C
Li et al[28]	16/36	13/36		4.42	1.23 (0.70–2.17)	C
Li et al[29]	9/20	7/20		2.38	1.29 (0.06–2.77)	C
Chen et al[16]	13/28	9/27		3.11	1.39 (0.72–2.71)	C
Lv et al[24]	11/30	7/30		2.38	1.57 (0.71–3.50)	B
Wang and Zhang[33]	23/39	15/41		4.97	1.61 (1.00–2.61)	C
Wu et al[25]	26/39	17/44		5.43	1.73 (1.12–2.66)	C
Subtotal (95% CI)	268	275		34.18	1.30 (1.07–1.59)	
Total events: 129 (KLT), 102 (Chemotherapy)						
Test for heterogeneity: $\chi^2 = 6.17$, $df = 1$ ($P = 0.52$), $I^2 = 0\%$						
Test for overall effect: $z = 2.64$ ($P = 0.008$)						

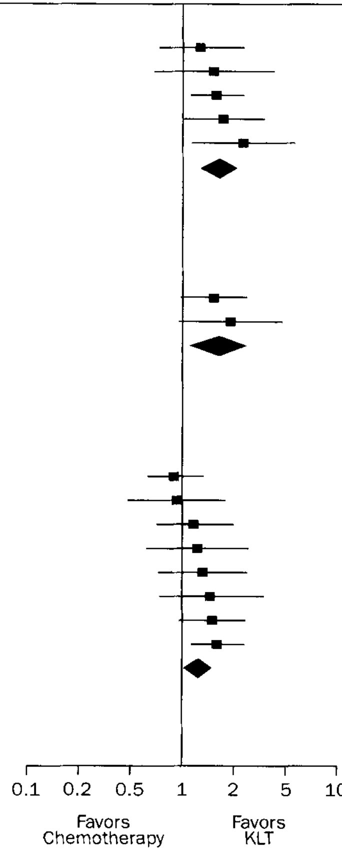

Figure 2. Meta-analysis forest plot of studies examining the effective rate of kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone. (continued)

Study or Subcategory	KLT, n/N	Chemotherapy, n/N	RR (fixed), 95% CI	Weight, %	RR (fixed), 95% CI	Quality*
HEP + KLT vs HEP						
Tang[17]	18/26	12/22		4.42	1.27 (0.80–2.01)	C
Subtotal (95% CI)	26	22		4.42	1.27 (0.80–2.01)	
Total events: 18 (KLT), 12 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 1.02$ ($P = 0.31$)						
CAP + KLT vs CAP						
Lin et al[20]	23/39	15/41		4.97	1.61 (1.00–2.61)	B
Subtotal (95% CI)	39	41		4.97	1.61 (1.00–2.61)	
Total events: 23 (KLT), 15 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 1.95$ ($P = 0.05$)						
KLT + NP or GP vs NP or GP						
Lu[23]	27/62	19/51		7.08	1.17 (0.74–1.84)	C
Subtotal (95% CI)	62	51		7.08	1.17 (0.74–1.84)	
Total events: 27 (KLT), 19 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 0.67$ ($P = 0.50$)						
KLT + MVP or EP vs MVP or EP						
Piao et al[12]	26/214	13/91		6.20	0.85 (0.46–1.58)	B
Subtotal (95% CI)	214	91		6.20	0.85 (0.46–1.58)	
Total events: 26 (KLT), 13 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 0.51$ ($P = 0.61$)						

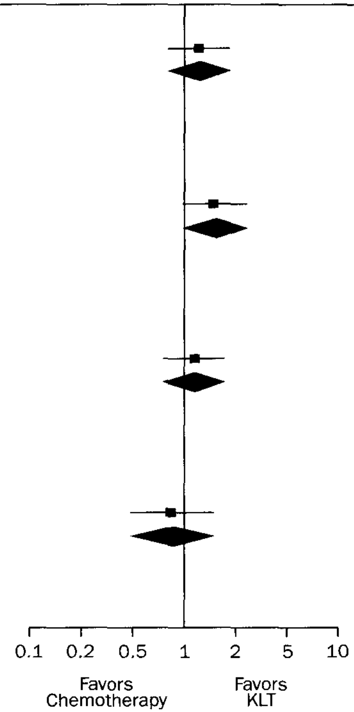

Figure 2 (continued). Meta-analysis forest plot of studies examining the effective rate of kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone. (continued)

Study or Subcategory	KLT, n/N	Chemotherapy, n/N	RR (fixed), 95% CI	Weight, %	RR (fixed), 95% CI	Quality*
MAP or MVP + KLT vs MAP or MVP						
Liu et al[19]	27/131	28/131		9.51	0.96 (0.60–1.54)	B
Subtotal (95% CI)	131	131		9.51	0.96 (0.60–1.54)	
Total events: 27 (KLT), 28 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 0.15$ ($P = 0.88$)						
KLT + CEP vs CEP						
Li et al[29]	18/32	13/32		4.42	1.38 (0.82–2.33)	C
Subtotal (95% CI)	32	32		4.42	1.38 (0.82–2.33)	
Total events: 18 (KLT), 13 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 1.23$ ($P = 0.22$)						
EP + KLT vs EP						
Huang et al[27]	23/53	11/23		5.21	0.91 (0.54–1.54)	C
Subtotal (95% CI)	53	23		5.21	0.91 (0.54–1.54)	
Total events: 23 (KLT), 11 (Chemotherapy)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 0.36$ ($P = 0.72$)						
Total (95% CI)	1069	909		100	1.34 (1.19–1.51)	
Total events: 415 (KLT), 284 (Chemotherapy)						
Test for heterogeneity: $\chi^2 = 20.66$, $df = 21$ ($P = 0.48$), $I^2 = 0\%$						
Test for overall effect: $z = 4.89$ ($P < 0.001$)						

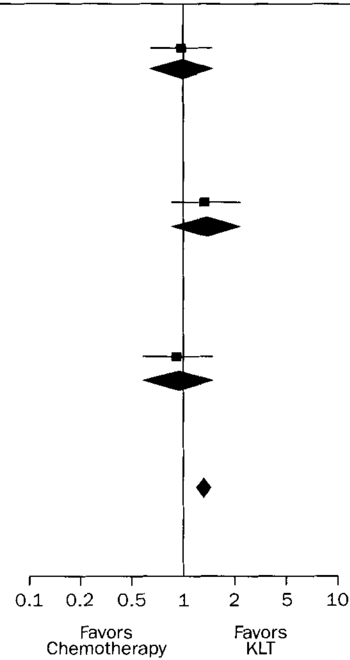

Figure 2 (continued). Meta-analysis forest plot of studies examining the effective rate of kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone. RR = relative risk; MVP = mitomycin + vindesine + cisplatin; GP = gemcitabine hydrochloride + cisplatin; NP = vinorelbine + cisplatin; HEP = hydroxycamptothecin + etoposide (VP-16) + cisplatin; CAP = cyclophosphamide + adriamycin + cisplatin; EP = cisplatin + VP-16; MAP = mitomycin + adriamycin + cisplatin; CEP = cyclophosphamide + VP-16 + cisplatin. *Per the Cochrane Collaboration,[11] the studies were assigned to 1 of the following 3 categories: A = all quality criteria met, low risk of bias; B = ≥1 of the quality criteria only partially met, moderate risk of bias; C = ≥1 of the quality criteria not met, high risk of bias.

cluded only 1 trial with sample sizes ranging from 39 to 214. These findings may be due to different chemotherapy regimens being associated with different response rates or to the sample size being too small to detect a difference.

Three trials[15,34,35] that did not perform ITT analysis reported that KLT improved the response rate. Yang et al[15] reported that 3 patients withdrew from the trial group (2 due to surgery or radiotherapy during the study period and 1 due to financial issues). In addition, 3 patients withdrew from the control group because they had undergone surgery or radiotherapy during the study. An and Yuan[34] reported that 4 patients discontinued therapy due to hearing disorder (2 patients), brain metastasis (1), or hepatic dysfunction (1); another 2 patients died. Ju et al[35] reported that 10 patients in the KLT group and 6 in the control group were lost to follow-up due to complete data being unavailable. The results of ITT analysis did not show statistical differences in the response rate between KLT plus chemotherapy and chemotherapy alone.

Quality-of-Life Improvement

The details of quality-of-life improvement are shown in **Figure 3**. Eighteen trials[12,14–20,22–24,26–28,31,32,36,37] reported the number of patients with NSCLC who exhibited an improvement of ≥10 points in their KPS score. Heterogeneity was found among subgroups ($P < 0.001$); therefore, the random effect model was used for total pooled analysis. Compared with chemotherapy alone, KLT injection plus chemotherapy was associated with an increase in the number of patients with NSCLC with a ≥10-point improvement in their KPS score (RR, 2.05; 95% CI, 1.60–2.64). We excluded trials with a quality grade of C and conducted a sensitivity analysis, which revealed concordant results (RR, 3.17; 95% CI, 2.39–4.20).

One study[26] found that KLT plus chemotherapy was associated with an increase in the number of patients with a ≥10-point improvement in KPS score. Our meta-analysis found that there was no statistically significant difference between the 2 groups. We found that the incorrect statistical method had been used in the study to analyze the data (ie, the t test was used to analyze dichotomous data).

Two other studies[15,18] found that KLT was associated with significant improvement in the KPS score in the absence of ITT analysis. Our ITT analysis showed that there was no statistically significant difference between the trial and control groups (**Figure 2**).

Symptom Improvement

Six trials[12,19,27,29,34,36] used improvement in symptoms as an outcome measure and reported the results. Three trials[12,19,36] all used the same symptom improvement scale. One trial[36] reported the number of patients whose symptoms resolved completely.

Only data from the 3 trials that used the same scale were pooled (**Table III**). The pooled analysis showed that KLT plus chemotherapy was associated with improvement in dyspnea and chest pain but not hemoptysis. For the improvement in cough, the findings from the fixed effect model suggest that KLT injection was effective (RR, 1.36; 95% CI, 1.11–1.67), but those from the random effect model did not find this

Study or Subcategory	KLT, n/N	Chemotherapy, n/N	Weight, %	RR (random), 95% CI	Quality*
MVP + KLT vs MVP					
Wu et al[26]	18/21	13/19	7.45	1.25 (0.88–1.78)	C
Li and Wang[14]	29/34	18/30	7.62	1.42 (1.03–1.97)	C
Chen[31]	21/30	10/34	6.01	2.38 (1.34–4.21)	C
Subtotal (95% CI)	85	83	21.08	1.52 (1.09–2.11)	
Total events: 68 (KLT), 41 (Chemotherapy)					
Test for heterogeneity: $\chi^2 = 4.06$, $df = 2$ ($P = 0.13$), $I^2 = 50.7\%$					
Test for overall effect: $z = 2.50$ ($P < 0.01$)					
EP + KLT vs EP					
Huang et al[27]	41/53	17/33	7.39	1.50 (1.05–2.16)	C
Subtotal (95% CI)	53	33	7.39	1.50 (1.05–2.16)	
Total events: 41 (KLT), 17 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect: $z = 2.20$ ($P = 0.03$)					
GP + KLT vs GP					
Deng et al[22]	11/21	5/22	4.25	2.30 (0.96–5.51)	B
Subtotal (95% CI)	21	22	4.25	2.30 (0.96–5.51)	
Total events: 11 (KLT), 5 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect: $z = 1.88$ ($P = 0.06$)					
NP + KLT vs NP					
Yang et al[15]	9/28	10/29	4.99	0.93 (0.45–1.95)	C
Xie et al[18]	20/43	17/14	6.54	1.20 (0.74–1.97)	B
Lv et al[24]	13/30	7/30	4.81	1.86 (0.86–4.00)	B
Li et al[28]	18/36	9/36	5.48	2.00 (1.04–3.84)	C
Chen et al[16]	19/28	8/27	5.60	2.29 (1.21–4.32)	C
Subtotal (95% CI)	165	166	27.42	1.55 (1.12–2.14)	
Total events: 79 (KLT), 51 (Chemotherapy)					
Test for heterogeneity: $\chi^2 = 5.11$, $df = 4$ ($P = 0.28$), $I^2 = 21.7\%$					
Test for overall effect: $z = 2.65$ ($P = 0.008$)					

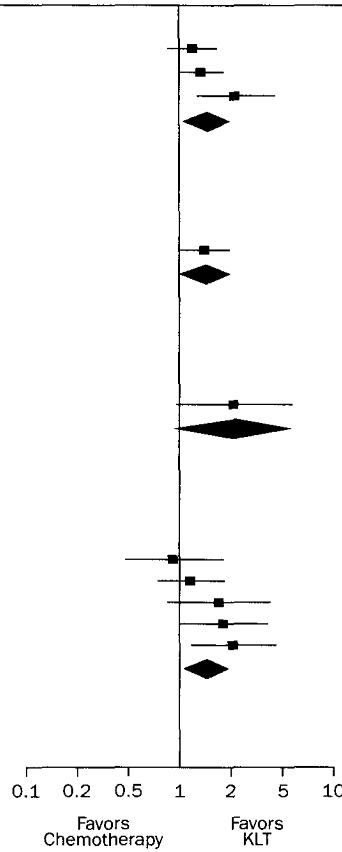

Figure 3. Meta-analysis forest plot of the number of non–small cell lung cancer patients with Karnofsky Performance Status score[8] improvement of ≥10 points of kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone. (continued)

Study or Subcategory	KLT, n/N	Chemotherapy, n/N	RR (random), 95% CI	Weight, %	RR (random), 95% CI	Quality*
HEP + KLT vs HEP						
Tang[17]	22/26	14/22		7.42	1.33 (0.93–1.90)	C
Subtotal (95% CI)	26	22		7.42	1.33 (0.93–1.90)	
Total events: 22 (KLT), 14 (*Chemotherapy*)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 1.57$ ($P < 0.12$)						
CAP + KLT vs CAP						
Lin et al[20]	24/39	8/41		5.38	3.15 (1.61–6.16)	B
Song et al[32]	20/26	3/20		3.40	5.13 (1.77–14.87)	C
Subtotal (95% CI)	65	61		8.78	3.62 (2.05–6.38)	
Total events: 44 (KLT), 11 (Chemotherapy)						
Test for heterogeneity: $\chi^2 = 0.59$, $df = 1$ ($P = 0.44$), $I^2 = 0\%$						
Test for overall effect: $z = 4.45$ ($P < 0.001$)						
KLT + NP or GP vs NP or GP						
Lu[23]	18/62	6/51		4.38	2.47 (1.06–5.75)	C
Wang et al[37]	12/42	4/38		3.48	2.71 (0.96–7.70)	C
Subtotal (95% CI)	104	89		7.86	2.56 (1.33–4.94)	
Total events: 30 (KLT), 10 (Chemotherapy)						
Test for heterogeneity: $\chi^2 = 0.02$, $df = 1$ ($P = 0.89$), $I^2 = 0\%$						
Test for overall effect: $z = 2.81$ ($P = 0.005$)						
KLT + MVP or EP vs MVP or EP						
Piao et al[12]	101/214	8/91		5.34	5.37 (2.73–10.56)	B
Subtotal (95% CI)	214	91		5.34	5.37 (2.73–10.56)	
Total events: 101 (KLT), 8 (*Chemotherapy*)						
Test for heterogeneity: not applicable						
Test for overall effect: $z = 4.87$ ($P < 0.001$)						

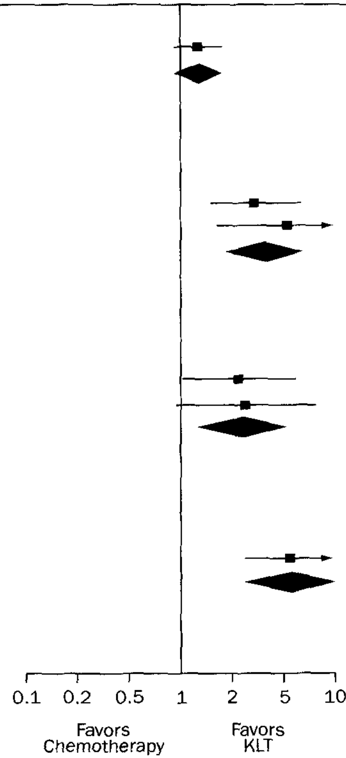

Figure 3 (continued). Meta-analysis forest plot of the number of non–small cell lung cancer patients with Karnofsky Performance Status score[8] improvement of ≥10 points of kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone.

(continued)

Study or Subcategory	KLT, n/N	Chemotherapy, n/N	Weight, %	RR (random), 95% CI	Quality*
MAP or MVP + KLT vs MAP or MVP					
Liu et al[19]	50/131	7/111	4.91	6.05 (2.86–12.81)	B
Subtotal (95% CI)	131	111	4.91	6.05 (2.86–12.81)	
Total events: 50 (KLT), 7 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect: $z = 4.71$ ($P < 0.001$)					
KLT + NIC vs NIC					
Zhong et al[36]	15/22	8/26	5.55	2.22 (1.16–4.22)	C
Subtotal (95% CI)	22	26	5.55	2.22 (1.16–4.22)	
Total events: 15 (KLT), 8 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect: $z = 2.42$ ($P = 0.02$)					
Total (95% CI)	886	704	100	2.05 (1.60–2.64)	
Total events: 461 (KLT), 172 (Chemotherapy)					
Test for heterogeneity: $\chi^2 = 57.65$, $df = 17$ ($P < 0.001$), $I^2 = 70.5\%$					
Test for overall effect: $z = 5.61$ ($P < 0.001$)					

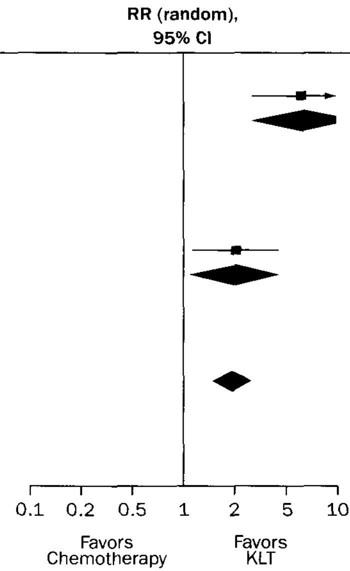

Figure 3 (continued). Meta-analysis forest plot of the number of non–small cell lung cancer patients with Karnofsky Performance Status score[8] improvement of ≥10 points of kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone. RR = relative risk; MVP = mitomycin + vindesine + cisplatin; EP = cisplatin + etoposide (VP-16); GP = gemcitabine hydrochloride + cisplatin; NP = vinorelbine + cisplatin; HEP = hydroxycamptothecin + VP-16 + cisplatin; CAP = cyclophosphamide + adriamycin + cisplatin; MAP = mitomycin + adriamycin + cisplatin; NIC = vinorelbine + ifosfamide + cisplatin. *Per the Cochrane Collaboration,[11] the studies were assigned to 1 of the following 3 categories: A = all quality criteria met, low risk of bias; B = ≥1 of the quality criteria only partially met, moderate risk of bias; C = ≥1 of the quality criteria not met, high risk of bias.

Table III. Improvement of symptoms associated with kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone.

Symptom	Treatment Group	Reference	Cases, n/N		Statistical Model	RR (95% CI)
			KLT	Chemotherapy		
Cough	KLT + MAP/MVP vs MAP/MVP	Liu et al[19]	49/106	41/98		1.10 (0.81–1.51)
	KLT + MVP/EP vs MVP/EP	Piao et al[12]	118/176	31/78		1.69 (1.26–2.26)
	KLT + NIC vs NIC	Zhong et al[36]	10/22	11/26		1.07 (0.57–2.04)
	Total				Fixed	1.36 (1.11–1.67)
					Random	1.31 (0.95–1.81)
Hemoptysis	KLT + MAP/MVP vs MAP/MVP	Liu et al[19]	29/41	23/34		1.05 (0.77–1.42)
	KLT + MVP/EP vs MVP/EP	Piao et al[12]	45/75	24/53		0.88 (0.65–1.17)
	KLT + NIC vs NIC	Zhong et al[36]	14/22	16/26		1.03 (0.67–1.60)
	Total				Fixed	0.97 (0.80–1.17)
					Random	0.97 (0.80–1.17)
Dyspnea	KLT + MAP/MVP + vs MAP/MVP	Liu et al[19]	36/70	15/49		1.68 (1.04–2.71)
	KLT + MVP/EP vs MVP/EP	Piao et al[12]	82/127	19/55		1.87 (1.27–2.75)
	KLT + NIC vs NIC	Zhong et al[36]	11/22	8/26		1.63 (0.80–3.31)
	Total				Fixed	1.77 (1.34–2.33)
					Random	1.77 (1.34–2.33)

(continued)

Table III (continued).

Symptom	Treatment Group	Reference	Cases, n/N		Statistical Model	RR (95 %CI)
			KLT	Chemotherapy		
Chest pain	KLT + EP vs EP	Huang et al[27]	15/53	4/33		2.33 (0.85–6.43)
	KLT + MAP/MVP vs MAP/MVP	Liu et al[19]	50/64	14/47		2.62 (1.66–4.15)
	KLT + MVP/EP vs MVP/EP	Piao et al[12]	72/92	9/40		3.48 (1.94–6.24)
	KLT + NIC vs NIC	Zhong et al[36]	17/22	8/26		2.51 (1.35–4.67)
	Total				Fixed	2.90 (2.11–3.98)
					Random	2.81 (2.06–3.84)
Fatigue	KLT + MAP/MVP vs MAP/MVP	Liu et al[19]	51/93	13/69		2.91 (1.71–4.91)
	KLT + NP vs NP	Li et al[29]	1/20	7/20		0.14 (0.02–1.06)
	Total				Random	0.75 (0.04–15.32)
					Sensitivity analysis	2.91 (1.72–4.91)
Anorexia	KLT + MAP/MVP vs MAP/MVP	Liu et al[19]	33/78	18/67		1.57 (0.98–2.53)
	KLT + MVP/EP vs MVP/EP	Piao et al[12]	104/165	19/70		2.32 (1.55–3.47)
	KLT + NP vs NP	Li et al[29]	2/20	8/20		0.25 (0.06–1.03)
	Total				Random	1.33 (0.62–2.86)
					Sensitivity analysis	2.91 (1.72–4.91)

RR = relative risk; MAP = mitomycin + adriamycin + cisplatin; MVP = mitomycin + vindesine + cisplatin; EP = cisplatin + etoposide; NIC = vinorelbine + ifosfamide + cisplatin; NP = vinorelbine + cisplatin.

effective (RR, 1.31; 95% CI, 0.95–1.81). Sensitivity analysis suggested that KLT was effective (RR, 1.40; 95% CI, 1.13–1.73). Therefore, KLT plus chemotherapy was considered to be effective in improving cough. One trial[36] also found that KLT injection plus chemotherapy was not associated with the complete resolution of symptoms.

For improvement in fatigue and anorexia, heterogeneity was found among trials; therefore, only the random effect model was used. Pooled analysis showed that KLT + chemotherapy was not effective in improving fatigue or anorexia, whereas sensitivity analysis demonstrated contrary results for both fatigue and anorexia (both, RR, 2.91; 95% CI, 1.72–4.91). Therefore, we considered that KLT was effective in improving fatigue and anorexia (**Table III**).

Adverse Events

The details of the AEs are shown in **Table IV**.

Bone Marrow Suppression

Eight trials[15,18,23,25,32,34,35,37] did not report the results with regard to leukopenia. Three trials[14,30,35] reported that the leukopenia rate did not meet the WHO grading criteria[8] for acute and subacute toxicity of anticancer drugs. Three trials[17,22,23] reported only the total incidence of bone marrow suppression. Thus we could not extract quantitative data. Twelve trials[12,13,16,19–21,26–30,33] reported the incidence of grade II to IV leukopenia. The pooled results of those 12 trials suggested that KLT injection plus chemotherapy was associated with a reduction in the incidence of leukopenia in both the fixed (RR, 0.29; 95% CI, 0.22–0.39) and random effect models (RR, 0.33; 95% CI, 0.22–0.48). Grade C trials were eliminated for the sensitivity analysis; the results of sensitivity analysis were in agreement with these results (RR, 0.19; 95% CI, 0.11–0.34).

A total of 11 trials[14,15,18,24,26,28,29,31,32,36,37] did not report their findings with regard to anemia. Six trials[17,22,23,25,34,35] reported bone marrow suppression findings but not anemia. The quantitative data of 8 trials[12,16,19–21,30,31,33] were extracted and a pooled analysis was conducted. No heterogeneity was found among the subgroups. The pooled results found that KLT plus chemotherapy was associated with a reduction in the incidence of grade II to IV anemia in both the fixed (RR, 0.54; 95% CI, 0.42–0.70) and random effect models (RR, 0.55; 95% CI, 0.40–0.76). The results of the sensitivity analysis were in agreement with this result (RR, 0.56; 95% CI, 0.43–0.72).

Seven trials[15,17,22,23,25,34,35] reported bone marrow suppression findings but not thrombocytopenia. Fourteen trials[14,15,18,20,24,26,28–33,36,37] did not report observations regarding thrombocytopenia. Four trials[12,13,16,19] reported the incidence of grade II to IV thrombocytopenia. These 4 trials were pooled; KLT plus chemotherapy was associated with a reduction in the incidence of thrombocytopenia in both the fixed (RR, 0.39; 95% CI, 0.21–0.71) and the random effect models (RR, 0.40; 95% CI, 0.21–0.78). A sensitivity analysis was in agreement with this result (RR, 0.34; 95% CI, 0.17–0.67).

Table IV. Adverse events associated with kanglaite (KLT) injection plus chemotherapy versus chemotherapy alone.

Adverse Event	Subgroup	Reference	Cases, n/N KLT	Cases, n/N Chemotherapy	Statistical Model	RR (95% CI)
Nausea/ vomiting (grade II–IV)	KLT + MVP vs MVP	Li and Wang[14]	11/34	25/30		0.39 (0.23–0.65)
	KLT + EP vs EP	Huang et al[27]	3/53	6/33		0.31 (0.08–1.16)
	KLT + GP vs GP	Lian et al[21]	0/50	0/50		–
	KLT + NP vs NP	Wang and Zhang[33]	5/39	10/41		0.53 (0.20–1.40)
		Li et al[28]	11/36	25/36		0.44 (0.26–0.75)
	Subtotal				Fixed	0.46 (0.35–0.59)
					Random	0.45 (0.35–0.59)
	KLT + HEP vs HEP	Tang[17]	6/26	6/22		0.85 (0.32–2.25)
	KLT + CAP vs CAP	Lin et al[20]	1/39	4/41		0.26 (0.03–2.25)
	KLT + NP or GP vs NP or GP	Lu[23]	18/62	31/51		0.48 (0.31–0.75)
	KLT + CEP vs CEP	Liu et al[30]	0/32	0/32		–
	Total				Fixed	0.44 (0.34–0.57)
					Random	0.44 (0.35–0.57)
Leukopenia (grade II–IV)	KLT + MVP vs MVP	Wu et al[26]	1/21	6/19		0.15 (0.02–1.41)
		Chu et al[13]	4/40	7/32		0.46 (0.15–1.43)
	Subtotal				Fixed	0.32 (0.12–0.85)
					Random	0.35 (0.13–0.94)
	KLT + EP vs EP	Huang et al[27]	11/53	18/33		0.38 (0.21–0.70)
	KLT + NP vs NP	Li et al[28]	6/36	20/36		0.30 (0.14–0.66)
		Wang and Zhang[33]	2/30	6/30		0.33 (0.07–1.52)
		Li et al[29]	4/20	7/20		0.57 (0.20–1.65)
		Chen et al[16]	9/28	14/27		0.62 (0.32–1.19)
	Subtotal				Fixed	0.44 (0.29–0.68)
					Random	0.47 (0.30–0.72)

(continued)

Table IV (continued).

Adverse Event	Subgroup	Reference	Cases, n/N KLT	Cases, n/N Chemotherapy	Statistical Model	RR (95% CI)
Leukopenia (grade II–IV) (cont'd)	KLT + CAP vs CAP	Lin et al[20]	4/39	12/41		0.35 (0.12–0.99)
	KLT + MVP or EP vs MVP or EP	Piao et al[12]	0/214	6/91		0.03 (0.00–0.58)
	KLT + MAP or MVP vs MAP or MVP	Liu et al[19]	4/131	32/111		0.11 (0.04–0.29)
	KLT + CEP vs CEP	Liu et al[30]	2/32	13/32		0.15 (0.04–0.63)
	KLT + GP vs GP	Lian et al[21]	1/50	2/50		0.50 (0.05–5.34)
	Total				Fixed	0.29 (0.22–0.39)
					Random	0.33 (0.22–0.48)
Anemia (grade II–IV)	KLT + MVP or EP vs MVP or EP	Piao et al[12]	10/214	14/91		0.30 (0.14–0.66)
	KLT + MVP vs MVP	Chu et al[13]	4/40	5/32		0.64 (0.19–2.19)
	KLT + GP vs GP	Lian et al[21]	0/50	3/50		0.14 (0.01–2.70)
	KLT + NP vs NP	Wang and Zhang[33]	0/30	2/30		0.20 (0.01–4.00)
		Chen et al[16]	1/28	2/27		0.48 (0.05–5.01)
	Subtotal				Fixed	0.33 (0.05–2.01)
					Random	0.35 (0.05–2.18)
	KLT + CAP vs CAP	Lin et al[20]	1/39	6/41		0.18 (0.02–1.39)
	KLT + MVP or MAP vs MVP or MAP	Liu et al[19]	49/131	61/111		0.68 (0.52–0.90)
	KLT + CEP vs CEP	Liu et al[30]	1/32	3/32		0.33 (0.04–3.04)
	Total				Fixed	0.54 (0.42–0.70)
					Random	0.55 (0.40–0.76)

(continued)

Table IV (continued).

Adverse Event	Subgroup	Reference	Cases, n/N KLT	Cases, n/N Chemotherapy	Statistical Model	RR (95% CI)
Thrombocytopenia (grade II–IV)	KLT + MVP or EP vs MVP or EP	Piao et al[12]	2/214	5/91		0.17 (0.03–0.86)
	KLT + MVP vs MVP	Chu et al[13]	1/40	5/32		0.16 (0.02–1.30
	KLT + NP vs NP	Chen et al[16]	3/28	3/27		0.96 (0.21–4.37)
	KLT + MAP or MVP vs MAP or MVP	Liu et al[19]	8/131	15/111		0.45 (0.20–1.03)
	Total				Fixed	0.39 (0.21–0.71)
					Random	0.40 (0.21–0.78)
Phlebitis (grade II–IV)	KLT + EP vs EP	Wu et al[26]	2/21	0/19		4.55 (0.23–89.08)
	KLT + HEP vs HEP	Tang[17]	2/26	0/22		4.26 (0.22–84.28)
	KLT + CAP vs CAP	Lin et al[20]	0/39	0/41		–
	KLT + NP vs NP	Wang and Zhang[33]	1/39	0/41		3.15 (0.13–75.08)
	KLT + GP vs GP	Deng et al[22]	9/21	3/22		3.14 (0.98–10.04)
	Total				Fixed	3.44 (1.30–9.15)
					Random	3.38 (1.28–8.89)
Hepatic dysfunction	KLT + GP vs GP	Lian et al[21]	4/50	9/50		0.44 (0.15–1.35)
	KLT + CAP vs CAP	Lin et al[20]	0/39	0/41		–
	KLT + NP vs NP	Wang and Zhang[33]	0/30	0/30		–
	KLT + MVP or EP vs MVP or EP	Piao et al[12]	0/214	0/91		–
	Total				Fixed	0.44 (0.15–1.35)
					Random	0.44 (0.24–0.81)
Renal dysfunction	KLT + GP vs GP	Lian et al[21]	0/50	0/50		–
	KLT + CAP vs CAP	Lin et al[20]	0/39	0/41		–
	KLT + NP vs NP	Wang and Zhang[33]	0/30	0/30		–

RR = relative risk; MVP = mitomycin + vindesine + cisplatin; EP = cisplatin + etoposide (VP-16); GP = gemcitabine hydrochloride + cisplatin; NP = vinorelbine + cisplatin; HEP = hydroxycamptothecin + VP-16 + cisplatin; CAP = cyclophosphamide + adriamycin + cisplatin; CEP = cyclophosphamide + epirubicin + cisplatin; MAP = mitomycin + adriamycin + cisplatin.

Nausea and Vomiting

Nine trials[14,17,20,21,23,27,28,30,33] reported the number of patients with grade II to IV nausea and vomiting. There was no statistical difference among the trials with regard to heterogeneity. Pooled analysis found that, compared with chemotherapy alone, KLT injection plus chemotherapy was associated with a reduction in the incidence of nausea and vomiting in both the fixed (RR, 0.44; 95% CI, 0.34–0.57) and random effect models (RR, 0.44; 95% CI, 0.35–0.57); however, sensitivity analysis suggested contradictory results (RR, 0.26; 95% CI, 0.03–2.25). Therefore, there was no statistical difference between KLT plus chemotherapy and chemotherapy alone with regard to improvement in nausea and vomiting. Deng et al[22] reported that 8 of 21 patients (38%) receiving KLT plus chemotherapy and 15 of 22 patients (68%) receiving chemotherapy alone experienced nausea and vomiting; however, they did not report the incidence of grade II to IV events.

Phlebitis

Pooled analysis of 4 trials[17,22,26,33] found a statistical difference in the incidence of phlebitis between KLT plus chemotherapy and chemotherapy alone in both the fixed (RR, 3.44; 95% CI, 1.30–9.15) and random effect models (RR, 3.38; 95% CI, 1.28–8.89). Piao et al[12] reported slight phlebitis in 10 patients that did not require treatment. Chu et al[13] reported slight phlebitis that could be avoided by IV infusion of KLT through subclavian vein puncture and catheterization. Yang et al[15] reported that phlebitis occurred occasionally prior to 1999; however, after 1999 phlebitis was not observed due to the use of catheterization. Liu et al[19] reported that 11 patients discontinued treatment due to severe phlebitis induced by low-quality raw materials used in the KLT injection. Chen[31] and Ju et al[35] reported that phlebitis occurred only occasionally. Lin et al[20] and Li et al[29] reported no incidence of phlebitis. The 14 other trials[14,16,18,21,23–25,27,28,30,32,34,36,37] did not mention phlebitis.

Hepatic and Renal Dysfunction

Pooled analysis of 4 trials[12,20,21,33] using the fixed model found that KLT plus chemotherapy did not decrease the incidence of grade II to IV hepatic dysfunction (RR, 0.44; 95% CI, 0.15–1.35). Five trials[12,20,31,33,35] reported no incidence of grade II to IV hepatic dysfunction. Fourteen trials[15–19, 23–25,27,30,32,34,36,37] did not mention hepatic dysfunction. Li and Wang[14] and Deng et al[22] reported the incidence of hepatic dysfunction but not specifically the incidence of grade II to IV events.

Three trials[20,21,33] reported no incidence of grade II to IV renal dysfunction. Li and Wang[14] reported that 5 patients in the KLT plus chemotherapy group and 22 patients in the chemotherapy alone group experienced renal dysfunction, but the incidence of grade II to IV events was not reported. Deng et al[22] reported the incidence of renal dysfunction but not specifically the incidence of grade II to IV events.

DISCUSSION

KLT injection is a product of traditional Chinese medicine; however, its effectiveness and safety in patients with NSCLC have been tested using Western methodology.[3]

Several controlled trials of KLT injection plus chemotherapy versus chemotherapy alone have been conducted in both Asian and American populations. However, because we included only RCTs, no RCTs of US populations were identified.

In total, this meta-analysis found KLT injection plus chemotherapy improved the response rate in these patients with NSCLC (RR, 1.34; 95% CI, 1.19–1.51). The subgroups of different chemotherapy regimens led to different conclusions. Subgroups of HEP, CAP, CEP, NP/GP, and MVP/MAP chemotherapy regimens included only 1 trial each; therefore, no statistical differences were found between the KLT plus chemotherapy and chemotherapy alone groups. On the other hand, the subgroups of MVP, GP, and NP regimens included >1 trial; statistical differences were found between the 2 groups. Therefore, it is possible that the sample size of a single trial was too small to test validity.

The effectiveness of KLT plus chemotherapy in improving the quality of life of patients with NSCLC was found to be highly significant (RR, 2.05; 95% CI, 1.60–2.64). Two trials[15,18] found positive conclusions, but the results of ITT analysis in our meta-analysis were negative, suggesting that the loss of patients to follow-up affected the results to some extent. One trial[26] concluded positive results by using inappropriate statistical methods, but the findings of our meta-analysis were negative. Therefore, the statistical method used was also a factor influencing the results.

KLT plus chemotherapy in this meta-analysis was associated with a significant decrease in the incidence of AEs, including grade II to IV leukopenia, anemia, and thrombocytopenia. This combination therapy was also associated with significant improvement in the symptoms of grade II to IV cough, dyspnea, chest pain, fatigue, and anorexia.

KLT injection plus chemotherapy was not associated with obvious toxicity or AEs. Some patients may experience nausea, low-grade fever, or occasional skin rash or phlebitis.[12–14,16,17,19–21,23,26–30,33] No significant hepatic or renal dysfunction was found in either KLT injection plus chemotherapy or chemotherapy alone group.

LIMITATIONS

Literature related to KLT therapy in patients with NSCLC was collected by manual and Internet search and by requesting data from pharmaceutical manufacturers. A formal data extraction table was designed to extract data for quantitative analysis. The accuracy of the data extraction was assessed using a second reviewer. The 26 trials included were all published in China. They included 2209 patients with NSCLC. The sample size of each trial varied from 40 to 305 patients. None of the trials had sample sizes determined a priori. The heterogeneity among subgroups might be attributed to differing sample sizes. We found that the positive effect increased with a bigger sample size.

Information about random sequence generation was available for only 10 trials,[12,13,18–24,35] while information about allocation concealment was not available for any of the included trials. Therefore, there was a high risk of selection bias and performance bias in this systematic review. Information about blinding was available for only 3 trials[12,13,35]; therefore, a high detection bias also existed in this systematic review. Only 6 trials[12,13,15,18,19,35] reported the number of patients who were lost to follow-up or the reasons they were lost to follow-up. Our ITT analysis reversed the original positive results in the case of 3 trials[15,25,35] that reported the response rate and 2 trials[14,17] that reported improvement in quality of life. In the other trials that did not report the status of loss to follow-up or withdrawal, a high withdrawal bias existed.

Only 4 trials[12,19,27,36] reported improvement of symptoms, including cough, hemoptysis, dyspnea, chest pain, fatigue, and anorexia. Overall, 11 trials[14,16,17,20,21,23,27–30,33] reported AEs occurring in the trial and control groups. The remaining 15 trials did not provide information about AEs. Four trials[12,19,27,36] reported the outcome of symptom improvement. Only 3 trials[17,22,23] reported the total incidence of bone marrow suppression. No data on leukopenia, anemia, or thrombocytopenia were available. Selection reporting outcome bias led to some unavailability of integrated results. No trial reported the outcome measure of mortality. These conclusions are also limited by the low quality scores of the included trials.

CONCLUSION

This meta-analysis found that, compared with chemotherapy alone, KLT injection plus chemotherapy improved the response rate, quality of life, and symptoms, and decreased the incidence of AEs in these patients with primary NSCLC.

ACKNOWLEDGMENT

This research received no support from industry.

REFERENCES

1. Molina JR, Adjei AA, Jett JR. Advances in chemotherapy of non-small cell lung cancer. *Chest.* 2006;130:1211–1219.
2. An introduction to kanglaite injection. http://www.kanglaite.com. Accessed June 27, 2007.
3. Nie LG, Pan ZB, Xu S, et al. Effects of extracts of *Semen coicis* on telomerase of squamous lung cancer cells. *Chin J Clin Pharmacol Ther.* 2003;8:419–421.
4. Yang H, Wang X, Linlin Y, Shu Z. Effects of kanglaite injection on reversing multiple drug resistance (MDR) of tumor cells. http://www.kanglaite.com. Accessed June 27, 2007.
5. Hu Y, Liang H, Gong WK, et al. The effect of kanglaite injection (KLT) on the proliferation and telomerase activity of rat mesangial cells. *Zhongguo Zhong Yao Za Zhi.* 2005;30:450–453.
6. Jiang XL, Zhang Liang, Xu ZY, Guo CH. Effect of kanglaite injection on angiogenesis. http://www.kanglaite.com. Accessed June 27, 2007.
7. Liu XM, Zhang MM, Li J, Qiu M. Chinese herbs for symptom palliation in patients with lung cancer. *Cochrane Database Sys Rev.* 2004;2:CD004698.
8. Department of Medical Administration of Ministry of Health of the People's Republic of China. Guideline of normal cancer diagnosis and treatment in China. 9th Branch. Main measurement indexes and statistical methods in normal cancer in China. Beijing, China: Beijing Medical University and China Union Medical University Press; 1991:11–15.
9. Park JO, Lee SI, Song SY, et al. Measuring response in solid tumors: Comparison of RECIST and WHO response criteria. *Jpn J Clin Oncol.* 2003;33:533–537.
10. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* 1981;47:207–214.

11. Alderson P, Green S, Higgins JP, eds. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. In: The Cochrane Library, Issue 1. Chichester, UK: John Wiley & Sons, Ltd; 2004.
12. Piao BK, Lin HS, Li PW, et al. Summary of phase III clinical trial of kanglaite injection in the treatment of primary bronchogenic pulmonary carcinoma. http://www.kanglaite.com. Accessed June 27, 2007.
13. Chu DT, Wang JW, Liu SX, et al. A phase III clinical study of kanglaite injection combined with chemotherapy (PVM Scheme) in the treatment of non-small cell lung cancer (NSCLC). http://www.kanglaite.com. Accessed June 27, 2007.
14. Li SW, Wang Y. Clinical study of Kanglaite combined with chemotherapy for non-small cell lung cancer patients. *Tumor.* 2002;22:84.
15. Yang SJ, Yao YM, Li YF, et al. Clinical observation of Kanglaite injection combined with chemotherapy for non-small cell lung cancer patients. *Chin J Integrated Traditional Western Med.* 2003;23:629.
16. Chen YZ, Li PP, Yan LF, et al. Effective observation of Kanglaite injection plus NVB and DDP regimen for non-small cell lung cancer patients. *Chin J Integrated Traditional Western Med.* 2003;23:629–630.
17. Tang JH. Clinical study of Kanglaite injection combined with HEP regimen for advanced non-small cell lung cancer patients. *Tumor.* 2002;22:83.
18. Xie XD, Zheng ZD, Gao YL, et al. A random control study: Effect of Kanglaite on life quality of patient with lung cancer in advanced stage. *Chin J Clin Rehabilitation.* 2003;7:672–673.
19. Liu JX, Liao ML, Yan DJ, Zhou JY. Kanglaite injection for the treatment of primary lung cancer: A phase II clinical trial. *Traditional Chin Drug Res Clin Pharmacol.* 1995;6:17–22.
20. Lin YH, Wang F, Chen P, Zhang JL. Combination of Kanglaite injection and CAP regimen chemotherapy in treatment of late non-small cell lung cancer. *J Qilu Oncol.* 2004;11:647–649.
21. Lian ZP, Lu YX, Hou EC, Wang X. Combination of GP regimen and Kanglaite in the treatment of advanced non-small cell lung cancer. *Chin J Lung Cancer.* 2006;9:74–77.
22. Deng SG, Wen SG, Wen SB, Chen AL. Clinical observation of Kanglaite injection combined with Gemzar and carboplatin for median and advanced non-small cell lung cancer patients. *Zhejiang Practical Med.* 2006;11:234–236.
23. Lu CD. Kanglaite injection combined with chemotherapy for advanced non-small cell lung cancer patients. *J Modern Oncol.* 2006;14:964–965.
24. Lv XY, Zhang YQ, Li QS. Clinical study on quality of life for chemotherapy combined with kanglaite in non-small cell lung cancer. *J Clin Pulmonary Med.* 2004;9:342–343.
25. Wu RL, Ou DB, Pan XJ. Clinical observation of Kanglaite injection combined with NVB and DDP for median and advanced non-small cell lung cancer patients. *Shaanxi Oncol Med.* 2002; 10:201.
26. Wu XH, Hua D, Sha LJ, Wu LL. Kanglaite injection combined with MVP regimen for non-small cell lung cancer patients. *J Qilu Oncol.* 2001;8:657–658.
27. Huang JY, Gao P, Wang XQ. Clinical observation of Kanglaite injection combined with EP regimen for advanced non-small cell lung cancer patients. *Tumor.* 2001;21:392.
28. Li ZG, Hu HY, Zhang JS. Observation on efficacy Kanglaite injection combined with chemotherapy in treating non-small cell lung cancer in aged patients. *Chin J Cancer Prev Treat.* 2003;10:405–406.
29. Li ZH, Lv JF, Zhou LZ. Clinical study of combined Kanglaite injection with chemotherapy in treatment of NSCLC. *Chin J Cancer Prev Treat.* 2005;12:1339–1340.
30. Liu YL, Sun XJ, Zhang J, Yang DC. Clinical observation of Kanglaite combined with CEP for non-small cell lung cancer patients. *Chin J Cancer Prev Treat.* 2003;10:895.

31. Chen ZP. Clinical study of Kanglaite injection combined with chemotherapy for 30 advanced lung cancer patients. *J Zhejiang College TCM*. 1999;23:35.
32. Song JL, Zhang LP, Liu ZW. Effect of combined therapy of Kanglaite on quality of life of middle-old aged patients with advanced non-small cell lung cancer. *Chin J Clin Rehabilitation*. 2002;6:1160–1161.
33. Wang ZX, Zhang ZG. Therapeutic effect of Kanglaite injection combined with chemotherapy on advanced non-small cell lung cancer. *Hebei Med J*. 2007;29:47–48.
34. An HJ, Yuan JZ. Clinical observation of Kanglaite combined with NC improve NSCLC of agedness. *Chin J Practical Chin Modern Med*. 2005;18:1205–1206.
35. Ju HB, Chen XJ, Wang BQ, et al. Clinical effect of Kanglaite plus PVM versus simple PVM for non-small cell lung cancer patients. *J Pract Oncol*. 2000;15:56–57.
36. Zhong YH, Liu H, Chen M. Clinical observation of Kanglaite combined with NIC for non-small cell lung cancer patients. *Shaanxi Oncol Med*. 2001;9:288.
37. Wang YL, Li DM, Xu H, et al. Combination of Kanglaite injection and chemotherapy for treatment of advanced non-small cell lung cancer. *Oncol Prog*. 2005;3:273–275.

ADDRESS CORRESPONDENCE TO: Youping Li, MD, Chinese Cochrane/ Evidence-Based Medicine Center, Chinese Journal of Evidence-Based Medicine, Periodical Press of West China Hospital of Sichuan University, No. 37 Guoxue Road, Chengdu, 610041, P.R. China. E-mail: ypl1949@yahoo.com.cn